REMARKS

The following remarks and attached Declaration of Dr. Saragovi are responsive to objection/rejections raised by the Examiner in the Final Office Action, dated March 17, 2008.

Status of the Claims

Claims 35 and 39 are currently under consideration in the application. Claim 35 is amended herein. Claims 1-29 and 31-34 are withdrawn from consideration. Claims 30 and 36-38 were canceled previously. Support for amended Claim 35 appears at least in original Claim 30 as well as at page 9, lines 25-30 in the specification as originally filed. The foregoing amendments were made without any intention to abandon any subject matter, but with the intention that one or more claims of the same, lesser, or greater scope may be pursued in a later application or in a continuation, continuation-in-part, or divisional application. The present amendment does not add new matter.

Rejections Under 35 U.S.C. §103

The Examiner has maintained the previous rejection of Claims 35 and 39 pursuant to 35 U.S.C. §103 as allegedly being unpatentable over Saragovi *et al.* (WO 97/21732) in view of Webb *et al.* (US 6,652,864) and Shih *et al.* (Cancer Immunol. Immunother. 1994; 38:92-98). Applicants respectfully traverses the rejection of Claims 35 and 39 under 35 U.S.C. §103.

Applicants have amended Claim 35 to recite a method of bypassing the p-glycoprotein pump in drug-resistant tumor cells mediated by p-glycoprotein pump, in a patient having a tumor comprising tumor cells, including drug-resistant tumor cells mediated by p-glycoprotein pump, using immunoconjugates as chemotherapeutic agents that can comprise three genus of monoclonal antibodies wherein the immunoconjugate binds to a specified cell surface antigen (*e.g.*, p75, TrkA; and IGF-1R polypeptide) and is internalized into the cell, bypassing the p-glycoprotein pump, to release the chemotherapeutic agent, whereby the chemotherapeutic agent bypasses the p-glycoprotein pump in drug-resistant tumor cells such that said tumor cells, including drug-resistant tumor cells mediated by p-glycoprotein pump, are selectively killed and the patient is thereby treated.

Applicants submit that none of the cited references teach or suggest, alone or in combination, a method of bypassing the p-glycoprotein pump in drug-resistant tumor cells mediated by p-glycoprotein pump, in a patient having a tumor comprising tumor cells. The Examiner states on page 5 of the office action that previous Claim 35 is drawn to a mechanism by which the compounds treat the tumors, and that the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. Applicants submit that this argument is rendered moot by the claim amendments presented herein, in which the claims have amended to recite a method of bypassing the p-glycoprotein in drug-resistance tumor cells, which method is not taught or suggested in the prior art.

The Examiner also states that Applicants must consider what the combined teachings of the references would have suggested to those of ordinary skill in the art. Applicants submit that Saragovi *et al.* teach treating tumors with 5C3, including treating a tumor by coupling a cytotoxic agent to the antibody. Webb *et al.* teach a binding agent that binds selectively to a neurotrophin receptor expressed in nerve cells (including 5C3 and MC192 specifically), a cleavable linker and a non-cytotoxic, therapeutic agent. Shih *et al.* teach an immunoconjugate of an anti-CEA antibody to doxorubicin for treating tumors. The references are silent as to methods of bypassing the p-glycoprotein pump. Taken together in combination, there is nothing in the references to suggest to a person of skill in the art that the immunoconjugates as claimed herein would bypass the p-glycoprotein pump. Indeed, Applicants note that Webb *et al.* teach conjugates with a *therapeutic, non-cytotoxic* agent, which could not be used to determine bypass of p-glycoprotein pump since a *cytotoxic* agent is required to bypass p-glycoprotein pump, and that Webb *et al.* teach delivery of therapeutic moieties specifically to *nerve cells*, which do not have multidrug resistance or a p-glycoprotein pump. A person of skill in the art, therefore, could not have a reasonable expectation based on the combined teachings of the references that the conjugated compounds could be used in a method of bypassing the p-glycoprotein pump. There is indeed nothing in the combined references that would lead a person of skill in the art to consider using the claimed conjugates to bypass the p-glycoprotein pump in drug-resistant tumor cells. In this regard, Applicants reiterate their former statement that the finding that the compounds of the

invention bypass the p-glycoprotein pump after binding to tumor cells and can be used in a method of bypassing the p-glycoprotein pump as claimed herein, was unexpected.

The Examiner objects on page 6 of the office action that objective evidence must be factually supported by an appropriate affidavit or declaration. In response, in support of this assertion, Applicants submit herewith in the Appendix a Declaration from the inventor, Dr. Uri Saragovi along with Dr. Uri's Curriculum vitae. Applicants submit that the method of bypassing the p-glycoprotein pump claimed herein could not have been predicted and represent an unexpected finding in the art.

In view of the foregoing, Applicants submit that the methods claimed herein are not obvious and respectfully request reconsideration and withdrawal of the 35 U.S.C. §103 rejection of the claims.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fee to Deposit Account No. 19-0741.

Respectfully submitted,

Date Sept. 17, 2008

By _____

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